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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/668,508	YOUNG ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 6/28/09, have been entered. Claims 52-53 are newly added; claims 37-53 pending and under current examination.

Claim Rejections - 35 USC § 112

The prior rejection of claims 14-17 and 33-35 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for new matter, is rendered moot in view of Applicants' cancellation of the claims. The newly added claims do not recite that the cells do not form tumors in an animal, which was the basis of this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-51 and newly added claims 52-53 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is rejection is maintained for reasons of record advanced in the prior Office action.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants argue that the claims are fully enabled and that the prior rejections of record relate to language and characteristics that are not present in the pending claims because the claims do not recite that the cells are pluripotent, and are not intended nor should be interpreted to cover ES cells. Applicants argue that they do not understand or agree with the Examiner's focus as to whether the cells are pluripotent, or that they express markers and have characteristics that fail to establish that they are pluripotent. Applicants argue that the novel cells of the claimed invention are unique and do not correspond to cells previously described, have their own unique characteristics, and characteristics previously ascribed to pluripotent cells, and embryonic cells, and are not precisely like any pluripotent or embryonic cells that have been prior isolated, described, anticipated or even suggested. Applicants argue that the Examiner should and must interpret the claims based upon the recited language and not on alleged characters or comparisons which are not in the present claim language and not relevant to the pending claims. See pages 7-9 of the Response.

Applicants argue that based upon a reading of the specification, including the teaching of the isolation and characterization of the claimed postnatal stem cells, the claims are enabled. Applicants argue that the cells are derived from postnatal cells or tissues, and thereby have the benefit of a straightforward and readily available source for isolation, and have characteristics thereby of postnatal cells, while having unique differentiative capacity only attributed to cells from an embryo, such as ES or EG cells. Applicants argue that the cells are quite unique and one of skill in the art could readily isolate, identify and use the postnatal stem cells, including from any animal species. The specification describes methods of isolating the cells, suitable exemplary markers and assays for characterizing the cells, including cell surface markers and differentiation assays and assessments, and characterizes the cells from species including rats, rabbits, mice, human and avian. Applicants argue that the isolation and characterization of the cells uses

standard methods and capabilities, and thus, coupled with the unique differentiative capacity of the claimed cells, which can be readily assessed and evaluated using known and described techniques, markers and assays, enables the skilled artisan to isolate and used the claimed postnatal stem cells. See pages 9-10 of the Response.

Response to Arguments. These arguments have been fully considered, but are not persuasive. In particular, MPEP §2164.08 states that, "When analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification." Similarly, MPEP §2111 states that, "During patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification."

In the instant case, Applicants have claimed isolated postnatal animal stem cells (or cultures of cells, methods of producing said cells) that are capable of self-renewal, differentiation to cells of endodermal, ectodermal, and mesodermal lineages, derived from postnatal animal cells or tissues and genetically engineered to express a gene or protein of interest. Therefore, turning to the specification to provide guidance for these cells, the as-filed disclosure describes these cells as pluripotent and embryonic-like stem cells. Thus, properly interpreted, the instantly claimed cells are reasonably interpreted in view of the specification's teachings as cells that are pluripotent and embryonic-like. The teachings of the specification provide guidance and definition for the claimed cells. The specification states that the cells are pluripotent, therefore, this is a necessary and inherent characteristic of the cells. The Examiner is not reading limitations into the claims but merely noting the fact that the disclosure teaches that the cells are pluripotent cells. Pluripotent cells have art-recognized characteristics which are not present in the instant cells. The instant specification teaches that the cells are embryonic-like pluripotent stem cells, which are capable of differentiation to cells of any layer e.g., endoderm,

mesoderm, ectoderm, or notochord, that they can be stimulated to proliferate, capable of extended self-renewal as long as they remain lineage committed. See page 36, lines 5-11. The working examples of the specification show that the cells can express markers of various cell types, including markers for endodermal, ectodermal, and mesodermal lineage (see, for example, p. 161, lines 22+). Although the specification teaches marker analysis and limited morphological analysis, there is no functional analysis of the resultant cells such that the specification makes clear that the postnatal stem cells are capable of forming cells from all three lineages that are capable of function as such cells. For example, the specification teaches evaluating cells with "spidery processes" and showed that the cells expressed markers of neuroectodermal origin (p. 164, lines 23+), but the specification provides no guidance to show that the neuronal cells functioned appropriately, for example, a neuron signaling through action potential. The expression of a marker may not be sufficient to identify a particular cell type. In the instant case the analysis of the cells produced by the pluripotent postnatal cells are only evaluated in terms of morphology and marker analysis. There is no guidance to show that the cells can differentiate into a specific cell type *in vivo*. Example 12, page 240 teaches the implantation of the rat pluripotent clone A2B2, and showed that there was no induction of graft-versus-host disease. However, there is no guidance to show that the cells were capable of differentiation *in vivo*, or that the cells that were differentiated *in vivo* were functional. The art recognized definition of a pluripotent cell is that it is capable of differentiation into cells of all three lineages, both *in vitro* and *in vivo*. Example 15 of the specification teaches sublethal irradiation of NOD/SCID mice and injection of CT3F PPELSC cells in the mice. It was found that approximately 0.5% of the bone marrow contained human Class I positive cells, and the spleen and peripheral blood contained no human cells (p. 246, lines 15+). At most, this example provides guidance to show that the cells

can form cells of hematopoietic lineage, but does not provide guidance to show that these cells can form cells of all three germ lineages *in vivo*.

The specification teaches that the cell of the claimed invention is a cell that is capable of self-regeneration and differentiation of cells of endodermal, ectodermal and mesodermal lineages. See page 33, 1st ¶. The specification contemplates that these cells are ES-like cells and pluripotent, and thus, broadly interpreted, the claims, as written encompass pluripotent cells, which are art-recognized to have specific qualities. See, for example, Thomson, cited previously. Additionally, the Examiner reiterates that the characterization Applicants' cells are pluripotent is not predictable, as stated previously, and additionally, because the cells express markers that fail to uniquely identify pluripotent stem cells, such as embryonic stem cells, because these markers as expressed in other cell types. The Examiner presented these arguments in the prior Office actions. In particular, the cells that the specification teaches expresses markers in EC cells, which are not expressed in ES cells, and further, it is noted that EC cells are different than ES cells in various ways, including differentiation potential. Additionally, the specification teaches that the cells express alkaline phosphatase, however, this marker fails to particularly identify a single cell type because this marker is expressed in other cell types (see Pera, Eiges, Gerecht-Nir, cited previously). Similarly, the specification teaches that the claimed cells express SSEA-4 (indicated by MC-813-70). See Table 7. Although SSEA-4 is a marker that is expressed in human ES cells, it is also expressed in mesenchymal stem cells; see Gang (cited previously). Therefore, these markers fail to specifically characterize a particular cell.

With regard to the isolation of the claimed postnatal cells from various animal species, the Examiner interprets the working examples as follows: Applicants appear to discuss two distinct cell types, a "pluripotent mesenchymal stem cell" and a "pluripotent embryonic-like stem cell". A pluripotent mesenchymal stem cell, as defined by the specification is a cell that is capable of self-renewal or

differentiation into any particular lineage within the mesodermal germ layer (see p. 37, lines 7+). A pluripotent embryonic-like stem cell is a lineage uncommited cell that can produce cells from endodermal, ectodermal and mesodermal lineages (see pages 35-36). Thus, working examples 1-5, relate to production of a pluripotent mesenchymal stem cell, which is not the subject of the instant invention. Example 7 relates to the isolation of human mesenchymal stem cells, including the cell lines CM-SkM, CF-SkM (human dermal fibroblast cell line), PAL#3 and PAL#2 (see p. 130 and p. 131, lines 30+). Example 8 relates to identification of progenitor an pluripotent stem cells from these human cell lines and it was found that insulin and dexamethasone differentiation studies resulted in cells that expressed markers characteristic of muscle, fat, cartilage, bone, connective tissue, endothelial cells, adipocytes (see p. 153, lines 9-15). Referring to the definition of a 'pluripotent mesenchyaml stem cell', these cells appear to be cells from the mesodermal germ layer (see p. 37, lines 10+). Thus, Example 8 appears to identify cells that would be considered pluripotent mesenchymal stem cells, which are distinct from the pluripotent postnatal stem cells which are instantly claimed.

The working examples that relate to the claimed cells appear to be Examples 9-16. In the instant case, Example 9, two human cell lines, CF-NFDF2 and PAL 3 cells were incubated with insulin and dexamethasone and the resultant differentiated cells were analyzed. The specification teaches that these cells had marker expression and morphology consistent with ES cells (p. 161, lines 4-14). Example 10 teaches expression analysis of pluripotent stem cells; however no species of animal is recited (see p. 182, lines 10+). It appears that Example 10 is a putative example, and Table 13 provides guidance for potential histological, function, immunological and cDNA probe markers that might be utilized in characterizing cell types (see p. 182, lines 4-5). Example 11 relates to utilizing a rat skeletal muscle cell line, Rat A2B2 (see p. 226, lines 15+) and the morphological, histochemical and immunocytochemical analyses of the putative embryonic-like

stem cells (see p. 228+). This example teaches that cells exhibiting markers for ectodermal, mesodermal and endodermal lineages were observed (p. 232, lines 15-18, for example). Example 12 relates to utilizing the same rat A2B2 cell line and implanting the cell line into outbred Sprague-Dawley rats to show that the cells do not induce a graft-versus-host response in the rats (see p. 240). Example 13 relates to the isolation of rat and mouse pluripotent cells, which are capable of differentiation into mesodermal and neuronal phenotypes. Notably, this Example does not show differentiation of the purported pluripotent cells into cells from all three cell lineages (see p. 241, lines 16-20). Thus, the cells in this example do not relate to the instantly claimed cells. Example 14 relates to the isolation of human stem cells (p. 242). These cells are designated pluripotent mesenchymal stem cells (PPMSCs) and pluripotent embryonic-like stem cells (PPELSCs). It is noted that claim 52 recites that the postnatal human stem cell expresses CD10. Careful inspection of this working example teaches that PPELSCs (the cells that relate to the instant invention) are negative for CD10 (see p. 243, line 18), this is appears that the cells taught in Example 14 do not relate to the cells claimed in claim 52 and its dependent claims, which require expression of CD10. Example 15 relates to utilizing human pluripotent stem cells to reconstitute the hematopoietic system of NOD/SCID mice (see p. 244). Example 16 relates to postnatal rat skeletal muscle cells (rat A2B2) and the transfection of these cells. Example 17 relates to a putative example to use retroviral vectors to deliver genes to pluripotent stem cells and test the ability of these cells to maintain their pluripotentcy. There are no specific results regarding this example.

Thus, in summary, the specification teaches, at the very most, isolation of two human cell lines (CF-NFDF2 and PAL 3) and a rat cell line (rat A2B2) that fulfill the limitations of the claims, contrary to Applicants' assertion that the claimed cells have been isolated from other species, such as rabbits and avians. The claims are not limited to any species of animal.

Rejection

The specification teaches that the pluripotent embryonic-like stem cells are isolated from various postnatal tissues and the cells were analyzed for differentiation capacity and expression of various markers. In particular, the specification teaches analysis of CF-NHDF2 (a dermis cell line), was incubated with dexamethasone and insulin for 45 days and examined morphologically, immunochemically and histochemically. See Example 9, p. 160. Additionally, the cell lines CM-SKM1 and CF-SkM2 were analyzed. The specification teaches that the cells were evaluated for alkaline phosphatase expression (indicating pluripotency), as well as extended capabilities for self-renewal, high levels of telomerase activity and induced differentiated cell types showing phenotypic markers for various tissue types. The specification further teaches that that these results indicate that the cells are pluripotent, embryonic-like stem cells. Tables 6-10 teach various markers that were tested, in particular, embryonic markers SSEA-1, SSEA-3, SSEA-4, H-CD34, H-CD66, and alkaline phosphatase were tested.

Furthermore, the claims are broadly directed to cells from any species, thus, there is no teaching, with regard to expression markers from cells other than human. Thus, although specification has shown that the claimed cells express alkaline phosphatase and SSEA-4, this does not provide sufficient guidance to show that these cells are pluripotent. The claims do not meet the definitions for a pluripotent cell, as set forth by the cited art above.

With regard to claim 46 and 52, wherein the cells express SSEA4 and CD10, Applicants are referred to the prior Office actions, which shows that pluripotent cells, such as ES cells, have specific characteristics, including differentiation potential, morphology, as well as specific cell markers, which define these cells. The claims are broadly directed to cells from any species, thus, there is no teaching, with regard to expression markers from cells other than human. CD10 is also expressed in various cell types. Applicants' cells would not be considered pluripotent, because

they express markers and have phenotypes and characteristics that fail to establish that they are pluripotent. It is unclear what type of cell(s) are encompassed by Applicants' cells because they do not possess many of the art-recognized characteristics of pluripotent cells. The characterization of a cell as pluripotent not only refers to its differentiation potential, but specific markers that serve to define these cells.

Accordingly, in view of the lack of teachings or guidance provided by the specification, with regard to the identification and characterization of the claimed cells, the state of the art, which clearly shows that using particular markers fails to establish or uniquely identify ES cells, it would have required undue experimentation for one of ordinary skill in the art to make and use the claimed cells.

Claim Rejections - 35 USC § 112

The prior rejection of claims 41-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of Applicants' amendment to the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 37, 38, 40-43, 45, 48, 49, 51 stand rejected under 35 U.S.C. 102(b) as being anticipated by Capecchi *et al.* [**Scientific American**, 270(3):34-41 (1994), of record].

Applicants' Arguments. Applicants traverse this rejection and argue that Capecchi does not teach the limitations of the claims because the instant cells are isolated from postnatal animal cells, and not derived from a mouse embryo. Applicants argue that that Capecchi describes targeted gene replacement in mice which requires germline transmission of the cells, whereas this could not be accomplished as described with a postnatal cell. Applicants argue that there exists a well recognized dogma of difference between an ES cell and a postnatal cell or tissue. Particularly, ES cells can spontaneously differentiate, form disorganized and heterogeneous gatherings of cells and form teratomas, whereas the instant cells do not have these characteristics. Applicants argue that this is a scientifically recognized and relevant distinction and should be taken as unanticipated and patentable distinct. Applicants argue that one of skill would readily acknowledge that the postnatal stem cells are absolutely distinct from the prior art. Applicants argue that the skilled artisan would note, upon reading and reviewing the culture studies and the animal *in vivo* experiments in the specification, that the post natal animal stem cells are distinct and not anticipated by the ES cells, such as those taught by Capecchi. Applicants argue that the postnatal stem cells do not act per se like ES cells, which establishes their difference and relative usefulness versus previously described ES or EG cells (see pages 13-14).

Response to Arguments. Applicants' arguments have been considered but are not persuasive. The arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01. Applicants have not provided an appropriate affidavit or declaration supporting that the cells of the instant invention cannot be used in methods such as those taught by Capecchi. There is no evidence of record to show

that the instant cells cannot contribute to the germline, because these experiments have not been done. Thus, Applicants' arguments regarding germline transmission are not on point because the specification is silent regarding this characteristic. Applicants point to various places in the specification in order to support the argument that the claimed cells are distinct from Capecchi's ES cells. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus, properly interpreted, the claimed cells require three structural elements: 1) self-renewal; 2) capability of differentiation to cells of endodermal, ecodermal and mesodermal lineages and 3) are genetically engineered to express a gene or protein of interest. Capecchi's cells fulfill this limitation. The term "postnatal" does not impart a patentable distinction between the claimed cells and Capecchi's cells. Applicants are encouraged to amend the claims to distinguish the claimed cells from that which is taught by the art.

Rejection

It is noted that the limitation in the claims that the cells are isolated from a postnatal source fails to distinguish the claimed cells from the cells of the art. The cells taught by Capecchi have the exact same characteristics as the required by the instantly claimed cells (*i.e.,* capable of self-renewal and differentiation to cells of endodermal, ectodermal and mesodermal lineages). The claims are not distinguished from the art.

Capecchi teach the inactivation of target genes by homologous recombination, and the insertion of a *neo* resistance gene, which serves as a positive selection marker in mouse ES cells. See Figure, p. 36. They teach that the ES cells are then cultured and grown into surrogate mothers to generate chimeric mice. See p. 38, Figure. Note that the claimed cells are not distinguished from those taught by Capecchi. Capecchi fulfills the limitations of the claims (the differentiation to cells of any endodermal, ectodermal, mesodermal lineage) by showing the generation of

mice; further, the methods of producing the genetically engineered cells are also anticipated by Capecchi because they teach transfection of pluripotent embryonic-like stem cells. Accordingly, Capecchi anticipate the claims.

Claims 37, 40-43, 45, 48, 49, 51 stand rejected under 35 U.S.C. 102(b) as being anticipated by Piedrahita *et al.*

Applicants' Arguments. Applicants argue that Piedrahita do not anticipate the claimed invention because the cells taught by Piedrahita are not postnatal cells, *i.e.*, cells that are isolated after birth. Piedrahita's cells are derived from embryonic tissue, and in particular, are primordial germ derived (see page 16 of the Response). Applicants argue that the claimed cells are simply not anticipated by the prior ES/EG or PGC cell art because there is nothing in the teaching of Piedrahita that anticipates postnatal animal stem cells capable of self-renewal, differentiation of endodermal, ectodermal and mesodermal lineages, and because the instantly claimed cells are isolated from postnatal cells or tissues and are not from embryonic tissue. Applicants provide teachings from the specification in attempts to distinguish the instant cells from that of the art, particularly with regard to the source of the cells (postnatal versus embryonic). See pages 16-17 of the Response. Applicants argue that Piedrahita's cells are isolated from a porcine fetus and have embryonic nature and character, whereas the instant cells are derived from postnatal tissue. Applicants argue that similarly to the arguments above, there is a well recognized dogma of difference between an ES cells and a postnatal cell or tissue and there is notation or indication of the characteristics of spontaneously differentiating, forming disorganized and heterogeneous gatherings of cells in culture and forming teratomas *in vivo.* See p. 1819 of the Response.

Response to Arguments. These arguments have been fully considered, but are not found to be persuasive. The art of Piedrahita anticipates the claims because it teaches each and every limitation found in the claim regarding 1) self-renewal; 2)

capability of differentiation to cells of endodermal, ecodermal and mesodermal lineages and 3) are genetically engineered to express a gene or protein of interest. The term "postnatal" does not impart a patentable distinction between the claimed cells and Piedrahita's cells because Piedrahita's cells fulfill what is instantly claimed. Applicants are encouraged to amend the claims to distinguish the claimed cells from that which is taught by the art.

Rejection

Piedrahita teach the generation of transgenic porcine chimeras using primordial germ cells (PGCs)-derived colonies. In particular, they teach the isolation of the PGCs from 25-27 day old pig fetuses, (p. 1321, 2nd column, Methods & Materials), they show the ability of the PGC to survive and proliferate in an undifferentiated state (see p. 1322, 1st column, AP Staining), the ability of the PGCs to differentiate into embryoid bodies (p. 1322, 1st column), the transformation of PGCs by electroporation using a plasmid that contained humanized GFP (p. 1322, col. 1-2) and the generation of chimeric pig fetuses and pigs using the transformed PGCs.

Piedrahita *et al.* anticipate the claimed invention because the PGCs they teach are capable of differentiation into the three germ layers (as evidenced by both the generation of embryoid bodies and the generation of chimeric pig fetuses and chimeric piglets). Chimeric animals, by definition, have some cells have cells that are contributed by the donor cells, and some from the cells of the recipient blastocysts. Piedrahita teach the analysis of transgene expression and show that the pigs expressed the transgene in different tissues, they teach that analysis of the developing fetuses suggests that although some may have germ line transmission, it would require that the chimeric cells contribute to the germ line. See p. 1328, 2nd column, 2nd full ¶, and p. 1329, 1st column, 2nd ¶. Accordingly, Piedrahita anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37-45, 47-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shamblott when taken with Sambrook *et al.* This rejection is maintained for reasons of record.

Applicants' Arguments. Applicants argue that the claimed stem cells are distinguished from Shamblott's PGCs and are not rendered obvious by the combination of the Shamblott and Sambrook references. Applicants argue that Shamblott's PGCs are absolutely distinct and do not anticipate or make obvious, Applicants' postnatal stem cells. Applicants argue that the addition of Sambrook to SHamblott's cells does not serve to make Applicants' cells or methods of isolating them obvious from Shamblott's cells. Applicants argue that the instant claims are isolated from postnatal stem cells and capable of self-renewal and differentiation to cells of endodermal, ectodermal and mesodermal lineages, genetically engineered to

express a gene or protein or interest. Applicants argue that Shamblott's cells are primordial germ cell derived and isolated from embryonic tissues. Applicants argue that similarly to the arguments above, these cells are not isolated from postnatal tissues. Applicants argue that Shamblott's human PGCs form EBs in culture and difficulties with complete cell disaggregation are noted, whereas the postnatal animal cells of the present invention do not demonstrate these qualities or characteristics. Applicants argue similarly to above, that there exists a well recognized dogma of difference between an embryonic cell or tissue and a postnatal cell or tissue. Applicants argue that ES and EG cells are recognized as spontaneously differentiating, forming disorganized and heterogeneous gatherings of cells in culture and forming teratomas, the instantly claimed cells do not have these characteristics. Applicants argue that one of skill in the art will immediately recognize and acknowledge the significance and distinction of the postnatal nature of the claimed cells, particularly and importantly when compared to an embryonic cell. Applicants argue that this is a scientifically recognized and relevant distinction and should be taken as unanticipated and patentably distinct.

Response to Arguments. These arguments have been considered but are not persuasive. In particular, simply noting that postnatal cells are distinct from embryonic-derived sources is not sufficient to distinguish the instantly claimed cells from that which is taught in the art. In the instant case, the claims only require three distinct structural elements: 1) self-renewal; 2) capability of differentiation to cells of endodermal, ecodermal and mesodermal lineages and 3) are genetically engineered to express a gene or protein of interest. Thus, Shamblott's cells fulfill these structural limitations. Applicants' arguments regarding other characteristics are not limitations in the claims. Applicants are encouraged to amend the claims to distinguish the claimed cells from that which is taught by the art.

Rejection

Shamblott *et al.* teach the generation of human pluripotent stem cells from gonadal ridges and mesenteries containing primordial germ cells [PGCs] and teach that embryoid bodies collected from these cultures revealed a wide variety of differentiated cell types, including derivatives of all three embryonic germ layers [see *Abstract*]. In particular, Shamblott *et al.* teach that gonadal ridges and mesenteries of 5 to 9 week old human fetuses and cells initially cultured on a layer of mouse STO fibroblast feeder layer. The cells formed embryoid bodies, which were collected and analyzed immunohistochemically [see pp. 13726-13727, *Materials & Methods*]. It was found that the embryoid bodies demonstrated derivatives of the three embryonic germ layers [see p. 13729, 2nd column and Table 1]. Note that Shamblott teach the pluripotent embryonic-like stem cells because the claims do not provide any requisite characteristics (*e.g.*, specific markers, etc.) of the claimed embryonic-like stem cells such that they would be distinguished from the cells taught by Shamblott. The claims recite that the embryonic-like stem cells are "derived from non-embryonic or postnatal animal cells or tissue;" however, this recitation does not differentiate them from the cells as taught by Shamblott. Further, the method claim has been included in this rejection because the cells as instantly claimed are not distinguishable from those taught in the art. The cells as taught by Shamblott fulfill the requirements of the claims because they are capable of differentiation to cells of each and any of endodermal, ectodermal and mesodermal lineages, and are capable of self-renewal.

Shamblott do not teach the transfection of the pluripotent stem cells to produce a genetically engineered pluripotent stem cell. However, prior to the time of the claimed invention, Sambrook teach methods of transfecting mammalian cells with any gene of interest [see 16.33-16.38]. Accordingly, in view of the combined teachings of Shamblott and Sambrook, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to use the PGCs, as taught by Shamblott and transfect them with any DNA of interest, with a

reasonable expectation of success. One of skill in the art would have been sufficiently motivated to make such a modification, as expression of proteins in mammalian cells can provide different purposes, as described by Sambrook on p. 16.3, such as for the expression of large amounts of protein of biological interest, or to study the biosynthesis and intracellular transport of proteins following their expression in various cell types.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 37-45, 47-51 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (**Science**, 282: 1145-1147, 1998, IDS). when taken with Sambrook *et al.* (cited previously).

Applicants provide no specific argument with regard to this rejection. The rejection is maintained.

Thomson teach the isolation of human ES cells. See p. 1145, col. 2. The cells are capable of maintaining an undifferentiated state and proliferate indefinitely, and have the potential to differentiate into derivatives of all three embryonic germ layers. They teach that the cells differentiated into cells of endoderm, mesoderm and ectoderm. Note that the claims fail to distinguish the claimed cells from the cells taught by Thomson. Thus, the method claim has been included in the rejection because the cells used in the method are not distinguished from those taught by Thomson. Thomson do not teach that the ES cells are genetically engineered to express a gene or protein of interest.

However, prior to the time of the claimed invention, Sambrook teach methods of transfecting mammalian cells with any gene of interest [see 16.33-16.38]. Accordingly, in view of the combined teachings of Thomson and Sambrook, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to use the pluripotent embryonic stem cells, as taught by

Thomson and transfect them with any DNA of interest, with a reasonable expectation of success. One of skill in the art would have been sufficiently motivated to make such a modification, as expression of proteins in mammalian cells can provide different purposes, as described by Sambrook on p. 16.3, such as for the expression of large amounts of protein of biological interest, or to study the biosynthesis and intracellular transport of proteins following their expression in various cell types.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632